Prenatal Diagnosis of Neural Tube Defects

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The embryonic forerunner of the human central nervous system is the neural tube, a structure which achieves tubular form prior to the 30th day of pregnancy.[1] It is believed that failure of normal tubular development in the primordial head region leads to anencephaly while a similar incident along the developing spinal cord results in one of the varying forms of spina bifida.

The use of alpha-fetoprotein (AFP) as a biochemical marker to aid in the prenatal detection of neural tube defect (NTD) was first introduced in the early 1970's and is currently most often applied to three specific pregnancy subgroups.[2,3] Families with a history of NTD may elect to undergo genetic counseling, diagnostic ultrasound, amniocentesis, and amniotic fluid alpha-fetoprotein (AFAFP) evaluation. Mothers with no history of congenital malformations may participate in maternal serum alpha-fetoprotein (MSAFP) screening which may lead to the clinical evaluations indicated in families with an NTD history. Finally, pregnancies undergoing genetic amniocentesis for other reasons may elect to have AFAFP evaluation to rule out open NTD. This report presents results relating specifically to the above three pregnancy subgroups.

Population A - Increased Risk Because of History of NTD

Nine hundred and ten pregnancies under evaluation were considered at increased risk for NTD because of the previous birth of an affected child or the existence of an affected first degree relative (Table I).

Open NTD [AFAFP > 5 S.D. Above Mean]	
Anencephaly	9
Open Spina Bifida	7
Encephalocele	1
Imperforate Anus	1
Situs Inversus	1
Cyclopia (Esophageal Atresia)	1
Hip Dysplasia	1
Chromosome Abnormalities	2
Closed Spina Bifida [MSAFP and AFAFP levels within normal limits]	1

Table I

All 16 fetuses with open NTD demonstrated AFAFP levels greater than 5 standard deviations above the mean and were diagnosed prenatally. A single skin covered lesion, not discovered until birth, was associated with normal MSAFP and AFAFP levels and represented the only false-negative result. No false-positive result leading to the termination of a normal fetus occurred. Of the other malformations noted only encephalocele was diagnosed prenatally.

Seven pregnancies with normal fetal outcome demonstrated AFAFP levels greater than 3 standard deviations above the mean. Five fell between 3 and 5 standard deviations, and 2 more than 5 standard deviations above the mean; 3 of the former samples and both of the latter were contaminated by fetal blood. All seven proceed to term on the basis of normal ultrasound and/or amniography.

Population B - Increased Risk Because of MSAFP Elevation

The Long Island regional AFP screening project identified 365 of 17,703 unselected pregnancies (2.1%) with an indication for further clinical evaluation. Twenty fetuses with NTD were detected (Table II), nineteen

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of which demonstrated AFAFP levels greater than 5 standard deviations above the mean. A single case of open spina bifida showed AFAFP levels between 3 and 5 standard deviations above the mean.

[AFAFP level > 5 S.D. above mean]	
Open NTD	
Anencephaly	10
Open Spina Bifida*	10
Gastroschisis	3
Omphalocele	1
Amniotic Band	1
Congenital Nephrosis	1
Microcephaly	1

Table II

Gastroschisis, omphalocele and amniotic band syndrome also were diagnosed. Congenital nephrosis and microcephaly both were associated with significant elevations in MSAFP and AFAFP levels, but detailed ultrasound evaluation and amniography revealed no NTD; these pregnancies continued to term.

Eight pregnancies of the amniocentesis group of 365 demonstrated elevated MSAFP and AFAFP levels and normal fetal outcome; all 8 had AFAFP samples between 3 and 5 standard deviations above the mean. Four of the 8 samples were contaminated by fetal blood. All 8 proceeded to term, as visualization showed no fetal abnormality.
Within the group receiving amniocentesis, no false-positive amniotic fluid results have led to the termination of a normal fetus, and no false-negative results have been observed. Of the total screened population of 17,703, the screening process has demonstrated an overall sensitivity of 91%.

Population C - Increased Risk for Reasons Other Than NTD History or MSAFP

Six thousand five hundred and four pregnancies considered at increased risk for reasons other than history of NTD or elevated MSAFP levels have been evaluated. Of this study population, 22 fetuses with NTD had AFAFP levels greater than 5 standard deviations above the mean (Table III).

[AFAFP level > 5 S.D. above mean]	
Open NTD	
Anencephaly	15
Open Spina Bifida	7
Encephalocele	4
Omphalocele	4
Hydrocephalus [MSAFP and AFAFP levels within normal limits]	2
Cyclopia	1
Congenital Nephrosis	1
Closed Spina Bifida [MSAFP and AFAFP levels within normal limits]	1

Table III

A single skin covered NTD had normal MSAFP and AFAFP levels and represented the only false-negative result. Within the population studied, no false-positive biochemical evaluations have led to the termination of a normal fetus.

Of the 12 other malformations within this group, the following were diagnosed prenatally: encephalocele (4), omphalocele (4), cyclopis (1), and congenital nephosis (1). In this case of congenital nephrosis, the family was at significant risk for recurrence. In spite of a normal ultrasound study, the family chose termination of the pregnancy on the basis of biochemical results. Post-mortem evaluation of the fetus confirmed the diagnosis.

Among the 6,504 pregnancies evaluated, 37 without fetal malformations had

AFAFP levels greater than 3 standard deviations above the mean. Of 30 samples showing AFAFP levels between 3 and 5 standard deviations above the mean, 11 were contaminated with fetal blood. All 30 pregnancies proceeded to term on the basis of fetal visualization by ultrasound and/or amniography. Of 7 samples with AFAFP levels greater than 5 standard deviations above the mean, 6 were contaminated by fetal blood. Of 6,504 pregnancies evaluated, one demonstrated an unexplainable AFAFP evaluation. This pregnancy continued to term on the basis of normal fetal visualization.

Conclusion

It would appear that a large body of information has accumulated supporting a rapid expansion of MSAFP screening and testing. Our views on this possibility as well as our specific recommendations for AFP program development have recently appeared.[4,5] We do not believe that rapid expansion toward nationwide screening within the obstetrical practice patterns characteristic of the United States will be a practical or safe means of proceeding. We do believe that AFP testing should be developed regionally on a pilot program basis to insure proper interprofessional communications, quality control, access to all needed clinical evaluations and in turn safe and effective testing. With proper program design and implementation, AFP screening and testing can be an important addition to prenatal care.

References

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